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Intraocular Pressure Changes Following Intravitreal Melphalan and Topotecan for the Treatment of Retinoblastoma with Vitreous Seeding

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Abstract

Purpose—To investigate the impact of intravitreal chemotherapy on intraocular pressure in children with retinoblastoma.

Methods—Retrospective study of ten eyes of ten retinoblastoma patients (7 males, 3 females, mean age 33.6 ± 9.4 months) with vitreous seeding injected with intravitreal melphalan and topotecan. Intraocular pressure (IOP) was measured with Tonopen at baseline prior to injecting and then repeatedly following each intravitreal injection.

Results—Mean pre-injection IOP was 8.2 ± 2.3 mm Hg (range 4.0 – 12.0 mm Hg). Mean IOP 1–30 seconds after intravitreal melphalan (first injection) was 45.4 ± 14.3 mm Hg. 89.5% of patients declined to 29 mm Hg in a mean 153.3 ± 97.5 seconds. Mean IOP 1–30 seconds after intravitreal topotecan (second injection) was 44.5 ± 11.0 mm Hg and decreased to 31.0 ± 5.0 by 150 seconds after injection. No significant relationship was found between age and post-injection IOP elevation. IOP exceeded calculated mean arterial perfusion pressure in four encounters.

Conclusions—Intravitreal chemotherapy caused a transient rise in IOP. Post-injection IOP elevations can reach levels that may exceed mean arterial pressure.

Keywords

intravitreal melphalan; intravitreal topotecan; intravitreal chemotherapy; vitreous seeding; retinoblastoma; intraocular pressure

Introduction

Vitreous seeding is the hallmark of high stage intraocular retinoblastoma and until recently the main reason for enucleation of eyes with retinoblastoma worldwide.^{1,2} Ophthalmic artery chemosurgery (OAC) and intravitreal injections of chemotherapy have, for the first time, reversed that. With OAC, 70% of eyes with vitreous seeding can now be saved and reports from many centers have confirmed that intravitreal injections of chemotherapy for eyes with vitreous seeds can increase that success rate.^{2–6}

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Intravitreal melphalan has emerged as an effective means of treating vitreous seeding for retinoblastoma, with an initial case series reporting ocular survival rates at 2 years exceeding 80%.⁵ These results have since been replicated at other institutions.^{6,7} Furthermore, longstanding unease that injecting a retinoblastoma eye risks extraocular extension along the needle track⁸ has been mitigated by recent reports.^{2,9} Accordingly, the number of groups worldwide using this treatment modality has been increasing.

While our group and others have reported on many of the adverse effects of intravitreal melphalan,^{1,2,10–13} there is only passing mention in the literature on the relationship between intravitreal chemotherapy and intraocular pressure (IOP). In the first description of intravitreal injection of thiotepa by Ericson and Rosengren in 1961, they observed that “when injecting 0.3–0.4 mm³ into the vitreous humor, an increase in pressure arises, disappearing after 15–20 minutes.”¹⁴ Over forty years later, Chévez-Barrios et al. noted increased intraocular pressure in patients receiving adenovirus-mediated thymidine kinase for eyes with vitreous seeding facing enucleation, without mention of volume of injection, or the magnitude or duration of IOP elevation.¹⁵ In a case series of twelve patients receiving intravitreal melphalan for vitreous seeding, Ghassemi and Shields wrote only that there “was no prolonged elevation of intraocular pressure” following intravitreal injection.¹⁰

There is a wealth of experience in the field of ophthalmology with intravitreal injections, particularly for the treatment of retinal vascular disease in adults. Many authors have demonstrated a transient increase in IOP following intravitreal injection of anti-VEGF therapy or triamcinolone acetonide.^{16–23} In addition, some eyes with retinoblastoma are now receiving two injections of two chemotherapeutic agents in the same session and nothing is

Because elevations in IOP exceeding arterial perfusion pressure are associated with short-term occlusion of the central retinal artery,^{24,25} decreased papillary and juxtapapillary blood supply,²⁶ and decreased axonal transport to the optic nerve head,²⁷ characterizing the relationship between intravitreal chemotherapy and IOP is of significant interest. We herein aim to describe the relationship between intravitreal chemotherapy and IOP in children with retinoblastoma, and to identify risk factors for pronounced elevations.

Material

This retrospective study included ten eyes of ten patients who received intravitreal melphalan and topotecan for advanced intraocular retinoblastoma with vitreous seeding at Memorial Sloan-Kettering Cancer Center between February 2015 and October 2015. After Institutional review Board Approval (IRB) at MSKCC data were collected from the medical record. The drug used, drug dose, drug volume, time of injection, intraocular pressures and age of the patient were collected. The study was Health Insurance Portability and Accountability Act (HIPAA) compliant. Research adhered to the tenets of the Declaration of Helsinki.

After induction of anesthesia with Sevoflurane (gas), the IOP was lowered by digital massage to 12 mmHg. The eye was then prepped in a sterile fashion, the lashes draped and the lid speculum placed. The injection location was selected in an area that was free of

tumor by ophthalmoscopy and by ultrasound biomicroscopy. Intravitreal melphalan (25 µg in 0.06 ml) was injected 2–3 millimeters posterior to the limbus with a 33-gauge needle using sterile technique. Prior to needle withdrawal, the injection site was sealed and sterilized with cryotherapy. After removal of the needle, serial measurements of IOP were taken with the Tono-pen (Reichert, Inc., Buffalo, NY). A second injection of topotecan (20 µg in 0.04 ml) was performed once IOP dropped below 32 mm Hg (except in one instance where IOP could not be lowered below 41 mm Hg); and again the injection site was sealed and sterilized with cryotherapy. IOP was again measured at multiple time points. Fundus exam was performed with indirect ophthalmoscopy following the second injection to evaluate for adverse events and patent vasculature.

Mean arterial pressure was calculated from the anesthesia record. Since time of injection was not recorded on the flowsheet, maximum measured IOP was compared to the lowest calculated mean arterial pressure for the duration of anesthesia.

Statistical analysis was performed using Prism (GraphPad Software, Inc, La Jolla, CA). IOP measurements were averaged for each patient over each time interval. Linear regression analysis was used to evaluate for correlation between age and IOP. The t test for paired samples was used to compare the IOP before injection with the IOP after injection at the various time intervals. Significance was accepted at $p < 0.05$.

Results

A total of ten eyes of ten patients (seven male, three female) totaling seventeen patient encounters (one patient had three encounters and five patients had two) were included in our study. The mean age was 33.6 ± 9.4 months (range 13.5–44.8 months). All patients received intravitreal melphalan for the treatment of vitreous seeding and all but one received intravitreal topotecan. Table 1 shows basic demographic and clinical data and results are summarized in Figs. 1 and 2.

Mean IOP immediately after the first injection (during the 1–30 second time interval) was 45.4 ± 14.3 mm Hg (mean increase 36.9 ± 13.7 mm Hg from baseline). Following the first injection, IOP declined to 29 mm Hg in a mean 153.3 ± 97.5 seconds in 89.5% of patient encounters. Of the remaining two patient encounters, one patient declined to an IOP of 32 mm Hg by 120 seconds and the other declined to an IOP of 41 mm Hg in 75 seconds before the second injection was given (Figure 1).

Mean IOP immediately after the second injection (during the 1–30 second time interval) was 44.5 ± 11.0 mm Hg (mean increase 18.2 ± 10.5), and decreased to 31.0 ± 5.0 by 150 seconds after injection (Figure 2).

No significant correlation was found between age and post-injection IOP elevation after either the first ($R^2 = .19$, $p = .0792$) or second ($R^2 = .07$, $p = .32$) injection.

IOP exceeded calculated mean arterial perfusion pressure on four occasions (Figure 3). On all four occasions, IOP decreased spontaneously to below arterial perfusion pressure in 22–74 seconds and no adverse events were recorded (see Table 2). Other than the pre-injection

digital massage, none of the patients in this study required additional intervention to lower IOP.

Discussion

Our study shows a transient and, in some instances, profound increase in IOP following intravitreal melphalan and topotecan for the treatment of retinoblastoma with vitreous seeding.

Transient elevations in IOP are common following intravitreal injections for the treatment of retinal vascular disease in adults, and previous authors have found a relationship between the initial elevation in IOP and the volume of the injection,^{20,23,28–30} needle gauge,^{19,29,31} and axial length.^{16,17,23} Anti-VEGF agents and triamcinolone acetonide are typically administered as 0.05 ml and 0.1 ml injections, respectively, amounting to an increase in the volume in the adult vitreous cavity of roughly 1.25–2.5%.³⁰ In our patients in this sample, we injected 0.06 ml of melphalan, which was followed in all but one case by 0.04 ml of topotecan. Since the size of the globe in children is smaller than that of adults,³² an injection of equal volume will represent a greater percentage increase in the volume of the vitreous. The corresponding increase in IOP may therefore be expected to be at least as large. Furthermore, the eye rapidly increases in size over the first few years of life, from an average axial length of 17.02 mm at birth to 22.07 mm by age 3.³³

The mean increase in IOP was smaller following the first injection (36.9 ± 13.7 mm Hg) than following the second injection (18.2 ± 10.5 mm Hg). One possible explanation is that the volume of the second injection was smaller than the volume of the first (0.04 ml compared to 0.06 ml). An alternative possibility is that the first injection triggered a compensatory response to accommodate the added volume that served to attenuate the post-injection increase from the second injection.

Although most eyes in this study followed a similar pattern of post-injection elevation in IOP followed by subsequent decline, there was considerable variation in both the magnitude of the elevation and time course of the decline. As such, it may not be possible to derive a standard pressure-volume equation, and clinicians will likely need to continue to measure IOP in order to quantify post-injection elevations and to guide management decisions. However, since IOP declined to less than 30 mm Hg in a mean 153.3 ± 97.5 seconds in this cohort of patients, the second injection can likely be safely administered approximately three to five minutes following the first injection.

Central retinal artery occlusion may develop when IOP exceeds arterial perfusion pressure.³⁴ In our study, four patients had post-injection IOP elevations that may have exceeded arterial perfusion pressure. In all four cases, IOP decreased to below arterial perfusion pressure in around one minute or less. Of note, retinal tolerance time to acute central retinal artery occlusion has been reported to be as long as 100 minutes in previous animal model studies,³⁵ significantly longer than occurred in any of the four patients in this study.

It could be suspected that elevated IOP might be a risk factor for post-injection reflux. Reflux of intraocular contents is deeply concerning when the contents could include viable

tumor cells. Previous authors have reported a higher incidence of post-injection reflux with larger needle size.³¹ In our practice we use 33-gauge needles and routinely use cryotherapy to seal the injection site. Recent studies have suggested that the risk of seeding of tumor cells along the needle track is extremely low.⁹ Further studies are needed to determine if elevated IOP increases the risk of this feared complication.

Limitations to our study include its retrospective nature, small sample size and use of Tonopen for the measurement of IOP. Although Goldmann applanation tonometry remains the gold standard for the clinical measurement of IOP in adults,^{36,37} it is difficult to perform on certain populations, including children and patients under anesthesia. Tonopen has been compared to Goldmann extensively in the literature. In general, Tonopen tends to be comparable to Goldmann in the normal pressure range, while overestimating IOP at low pressures and underestimating at high pressure.^{38,39}

In conclusion, we have demonstrated that intravitreal injection of melphalan and topotecan for the treatment of retinoblastoma with vitreous seeding is associated with transient and occasionally pronounced elevations in IOP that in some cases can exceed mean arterial pressure and thus risk occlusion of the central retinal artery. Further studies will be needed to determine if these acute elevations in IOP are of clinical significance.

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Figure 1.

Figure 2.

Figure 3.

Maximum IOP measured after intravitreal melphalan, maximum IOP measured after intravitreal topotecan, and mean arterial pressure for each patient encounter.

Table 1
Patient clinical and demographic data. Note that some patients were treated more than once.

Patient	Age at time of treatment (months)	Gender	Eye	R-E* ICRB†
1	41.7	M	OS	5B D
2	36.0	M	OS	5B D
	36.6			
	36.9			
3	38.9	M	OS	5B D
	40.1			
4	35.3	M	OS	5B D
5	20.9	F	OS	5B D
6	25.9	M	OD	5A E
	26.4			
7	23.3	F	OS	5A D
	23.6			
8	44.8	M	OS	5B D
	44.6			
9	41.3	F	OD	5B D
	42.0			
10	13.5	M	OD	5B D

* Reese-Ellsworth Classification
† International Classification of Retinoblastoma

Table 2

Maximum IOP recorded after intravitreal melphalan and topotecan and mean arterial pressure. Instances where the maximum IOP exceeded MAP are indicated with two asterisks.

Patient	Age (months)	IOPmax IVM* (mmHg)	IOPmax IVT [†] (mmHg)	MAP (calc.) [‡]	IOPmax>MAP?	Time to IOP<MAP (seconds)
1	41.7	42	67	58.3	**	30
2	36.0	49	22	59.3	-	-
	36.6	39	39	68.3	-	-
	36.9	42	21	65.0	-	-
3	38.9	41	43	60.7	-	-
	40.1	50	34	58.3	-	-
4	35.3	31	41	63.3	-	-
5	20.9	54	32	69.3	-	-
6	25.9	70	36	60.0	**	74
	26.4	85	N/A	60.0	**	32
7	23.3	54	54	60.0	-	-
	23.6	43	67	61.7	**	22
8	44.8	29	35	61.7	-	-
	44.6	41	34	63.3	-	-
9	41.3	41	30	71.0	-	-
	42.0	39	N/A	71.7	-	-
10	13.5	39	45	63.3	-	-

* Maximum IOP measured after intravitreal melphalan injection

[†] Maximum IOP measured after intravitreal topotecan injection

[‡] Mean arterial pressure (calculated)